Research Protocol

A double-blind randomized placebo-controlled clinical trial evaluating the efficacy of individualized homoeopathic medicines in treatment of knee osteoarthritis

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Abstract

Background: Rheumatologic problems including osteoarthritis (OA) are encountered frequently by the Complementary and Alternative Medicine (CAM) practitioners; however, scientific research has so far not provided evidences enough to support their efficacy or effectiveness. Few low-potency homoeopathic complexes produced significant treatment effects beyond placebo in OA, but the efficacy of individualized homoeopathic medicines (IH) remained under-researched. We intend to evaluate the efficacy of IH in comparison with placebo in treatment of knee OA in mutual context of standard physiotherapeutic measures.

Methods/Design: In this prospective, double-blind, randomized, parallel arm, placebo-controlled trial, patients diagnosed with knee OA as per the American College of Rheumatology (ACR) clinical/radiographic classification criteria will be randomized in 1:1 ratio to one of the two interventions as below:

Group 1: IH + Standard physiotherapy

Group 2: Placebo + Standard physiotherapy

Primary outcome is Knee injury and Osteoarthritis Outcome Score (KOOS). Secondary outcomes are 5 individual KOOS subscale scores – pain, other symptoms, activities of daily living, sport or

recreation and quality of life, and frequency of use of add-on paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs). The study endpoint is 6 months. All outcome scores will be obtained at baseline, after 3 and 6 months. The trial will require 132 patients in order to achieve 95% power for the primary endpoint. In accordance with CONSORT/ReDHoT guidelines, all comparative analyses will be conducted on intention-to-treat basis using SPSS.
Discussion: The outcomes from this trial will generate efficacy data of IH in treatment of knee OA.
Trial registration: CTRI/2018/04/013342; UTN: U1111-1212-2737

Keywords
Knee osteoarthritis; Homoeopathy; Knee injury and Osteoarthritis Outcome Score; Randomized Controlled Trial

INTRODUCTION

Osteoarthritis (OA) is a heterogeneous group of degenerative joint disease of multi-factorial origin, characterized by defective integrity and progressive loss of articular cartilage, sub-chondral bone remodelling, joint space narrowing and bone spur formation, as well as synovial inflammation [1]. Pain and functional impairment are the key domains of the burden of suffering experienced by people with OA that is of primary concern, and that burden can be significant, and taken together they often exert a significant reduction in quality of life [2, 3]. Since the last decade, recommendations for managing OA have focused persistently on relieving pain and stiffness and improving physical function as important goals of therapy [4, 5]. However, conventional drug therapy for OA successfully relieves pain only, alongside producing adverse gastrointestinal and cardiovascular effects, especially with long-term use [6]. Non-pharmacologic modalities strongly recommended for the management of knee OA were aerobic, aquatic, and/or resistance exercises as well as weight loss for overweight patients. Non-pharmacologic modalities conditionally recommended for knee OA included medial wedge insoles for valgus knee OA, subtalar strapped lateral insoles for varus knee OA, medially directed patellar taping, manual therapy, walking aids, thermal agents, tai chi, self management programs, and psychosocial interventions. Pharmacologic modalities conditionally recommended for the initial management of patients with knee OA included acetaminophen, oral and topical NSAIDs, tramadol, and intra-articular corticosteroid injections; intra-articular hyaluronate injections, duloxetine, and opioids were conditionally recommended in patients who had an inadequate response to initial therapy [7]. Although clinical guidelines recommend paracetamol as first line analgesic drug for knee OA, high quality evidence (meta-analysis of RCTs comparing the efficacy and safety of paracetamol with placebo) suggest Paracetamol as ineffective in the said condition, provides minimal short term benefit, but nearly four times more likely to have abnormal results on liver function tests compared to placebo. These results support the reconsideration of recommendations to use paracetamol for patients with knee OA [8]. Thus controversies regarding efficacy of the mainstay pharmacological agent and inadequacy of outcomes, people frequently refer to CAM therapies and homoeopathy.

Rheumatologic problems are among the most common conditions encountered by CAM practitioners [9-11]. Many patients use CAM therapies, including homoeopathy, to prevent, control and manage the pain of rheumatologic conditions [12, 13]. However, scientific research has so far not provided evidences solid enough to support the effectiveness of CAM as treatment options

for rheumatologic conditions including OA and has remained ambiguous. Reviews have remained contradictory in conclusions [14-21]. Few low potency homoeopathic complexes in the randomized controlled trials (RCTs) seemed to posses significant effects in OA [22], but the efficacy of individualized homoeopathy remained under-researched. Hence, based on small-to-moderate effect sizes for the wide range of symptomatic treatments, conventional medicine in personalized approach still remains the mainstay of treatment [23, 24]. A systematic review [25] of clinical trials of OA identified 8 controlled trials published during 1980-2013 [26-33] using 'complex homoeopathy' and 'combination formulae'. Overall results of the review showed homoeopathic complexes having a clear advantage in the treatment of OA; however, the evidence was not convincing enough to arrive at a definite conclusion because of methodological inconsistencies and insufficient trial reporting. An observational trial evaluated the individualized homoeopathic treatment of OA on 47 patients with promising results [34]. In another prospective observational trial, individualized homoeopathic medicines were found to have potential to improve the activities of daily living of OA patients by reducing pain and stiffness and limiting progress of the disease without any adverse systemic effects [35]. Recently, a prospective, parallel-arm, double-blind, randomized, placebo-controlled, feasibility study was conducted on 60 patients suffering from acute painful episodes of knee OA. In spite of a positive trend favoring homoeopathy, overall, homoeopathy did not appear to be superior to placebo [36]. However, any adequately powered RCT to examine the efficacy of IH in treatment of knee OA has not been conducted till date.

Aims and objectives:

- To evaluate the efficacy of individualized homoeopathy in comparison with placebo in treatment of knee OA
- To detect changes in the KOOS scores that incorporates pain and symptom severity, physical function, and quality of life elements
- To ascertain and shortlist the most frequently indicated homoeopathic medicines in treatment of knee OA

METHODS / DESIGN

Study design: Prospective, double-blind, randomized, placebo-controlled, two parallel arms trial with a 6 months' duration for each patient.

Trial registration: The study protocol is registered prospectively in Clinical Trials Registry – India (CTRI) vides reg. no. CTRI/2018/04/013342; secondary identifier UTN: U1111-1212-2737.

Study setting: Outpatients or inpatients of National Institute of Homoeopathy (NIH)

Selection of samples: Samples will be selected as per below mentioned eligibility criteria from the patients visiting the NIH outpatients or admitted inpatients. Formal effect size calculation was not possible on account of absence of any earlier study of similar design, i.e. no study till date tested the efficacy of IH in comparison with placebo keeping KOOS scores as the primary outcome, measured over 3 and 6 months. In a recent study in India, the mean (± standard deviation) of KOOS-pain subscale score of the 251 patients diagnosed with OA knee was reported to be 62.9 (± 18.1) [37]. We assumed the same standard deviation for our study sample and 20% reduction of the mean KOOS pain scores in the verum than control. Thus the assumed means and standard deviations of the control groups become 50.3 ± 18.1. Effect size (Cohen's d) was calculated to be 0.697. With this assumed effect size, keeping $\alpha = 0.05$, power = 95%, and allocation ratio of 1:1, to detect a significant difference between two independent means (two groups) of KOOS

pain scores through unpaired *t* test, calculated sample size becomes 110. Keeping a provision for 20% drop-outs, the target sample size becomes 132 (verum: 66, control: 66).

Inclusion criteria:

1. Age 50-70 years
2. Both sexes
3. Diagnosed knee OA as per American College of Rheumatology (ACR) clinical/radiographic classification criteria [38], (sensitivity 91%; specificity 86%):
    a) Knee pain
    b) At least 1 of 3: age more than 50 yrs, stiffness less than 30 min, and crepitus on knee motion
    c) Osteophytes on knee x-ray
4. Patients already undergoing regular oral or topical analgesics or NSAID therapy for painful episodes of OA, provided the medications are stopped completely at least 2 weeks prior study entry
5. Literate patients; ability to read English and/or Bengali language
6. Providing written informed consent

Exclusion criteria:

1. Severe degeneration of knee joint with marked joint narrowing, varus, or valgus deformity of knee (>12°), evidenced by imaging or other evidences and requiring surgical intervention
2. Non-ambulant patients
3. Self-reported joint disorders other than OA (e.g., inflammatory joint disease, specific arthropathy, severe axis deviations or instabilities, joint or skin infections, joint prostheses of the lower limbs)
4. Intra-articular injections within 2 weeks before study entry
5. Transplanted knees
6. Recent significant knee surgery within last 6 months
7. Patients who are too sick for consultation
8. Unwilling to take part and not giving consent to join the study
9. Unable to read patient information sheet
10. Diagnosed cases of unstable mental or psychiatric illness or other uncontrolled or life-threatening illness affecting quality of life
11. Pregnancy and lactation
12. Substance abuse and/or dependence
13. Self-reported immune-compromised state, and
    Undergoing homoeopathic treatment for any chronic disease within last 6 months

Criteria for discontinuing or modifying allocated interventions: Patients can be excluded from further participation within the study or withdraw themselves without having to provide any further reasons. Possible reasons for this therapy dropout are expected to be:

1. Withdrawal of the patient's consent
2. Consumption of drugs or, rather, medications which are not permitted during the duration of the clinical study
3. Deficient compliance of patients after the evaluation of the examining physician (regular and specified consumption of study medication)
4. A newly occurring condition which influences the efficacy of the study investigation or is contra-indicative to the intake of study medication or which needs to be treated with a medication which is not permitted as a concurrent medication during the study
5. Retroactive appraisal of either unfulfilled inclusion criteria or fulfilled exclusion criteria after the decision of the examining physician/leader of the clinical study

6. Medically necessary transfer of the patient to a different department/a different hospital during the study phase
7. Unexpected findings which make the continuation of therapy from an ethical or medical point of view unjustifiable; the decision will be made by the concerned physician

The complete study can be discontinued prematurely if it is perceptible early on that it cannot fulfill the aforementioned inclusion criteria. This includes:

1. The necessary recruiting numbers cannot be achieved
2. There are serious violations of the protocol
3. The documentation is incomplete or was deliberately filled out incorrectly and legal or ethical instructions are not met

Randomization: Permuted block randomization (fixed) method will be adopted to generate 13 blocks of 10 random numbers [13 × 10 = 130] and a single block of 2 random numbers to maintain 1:1 distribution ratio. Randomization chart will be generated by a 3rd party who will not be allowed to influence the study in any way. This chart will be made available to the pharmacist in strict confidentiality and will never be disclosed to the patients or doctors under any circumstances. The allocated code will be maintained till the end of the trial.

Blinding: Participants, the principal investigator and the co-investigators, the outcome assessors, and the pharmacist will remain blinded to the identity of the two treatment groups until the end of the study. Unblinding of individual participants through the investigator occurs in cases of SAEs.

Intervention:

- *Experimental arm*: Indicated homoeopathic medicines will be administered in centesimal potencies and in individualized dosage, as decided appropriate to the case or condition. Each dose consists of 4-6 cane globules no. 30 moistened with the indicated medicine (preserved in 90% v/v ethanol); to be taken orally on clean tongue with empty stomach; dosage and repetition depending upon the individual requirement of the cases. In addition to IH, standard physiotherapeutic measures will be advised. Duration of therapy: 6 months.
- *Comparator arm*: Placebo, indistinguishable from verum, will be administered thrice a day orally on clean tongue with empty stomach for 6 months. Each placebo dose will consist of 4-6 cane sugar globules no. 30 moistened with 90% v/v ethanol. In addition to this, standard physiotherapeutic measures will be advised. Duration of therapy: 6 months.

The homoeopathic medicines and placebo are provided by HAPCO® as bulk product. Both medicines and placebo are repacked in identical glass bottles and labeled with code, name of medicine and potency. These were dispended according to the randomization list provided to the pharmacist.

Selection of tools:

1. ACR diagnostic criteria for knee OA
2. Knee injury and Osteoarthritis Outcome Score (KOOS) (English and Bengali version)
3. Standardized data recording proforma
4. Repertorization software [RADAR®, version 10.0.028 (ck), Archibel 2007, Belgium]

Brief of procedure: Following preliminary screening using inclusion criteria and detailed screening using specified exclusion criteria, eligible patients will be recruited in the trial. Following that, outcome data (baseline KOOS) will be obtained. Coded identical containers will be used. Final

selection of the single individualized medicine will be based on case taking in adherence with the standard homoeopathic guidelines, analysis and evaluation of symptoms, miasmatic diagnosis, framing symptom totality, repertorization and consultation with Homoeopathic Materia Medica. Individualized dose will be selected on the judgment of susceptibility of the patients. Subsequent prescriptions will be generated according to Kent's observations, second prescription, and relevant homoeopathic principles and will be recorded in follow-up sheets.

Outcome assessment:

1. Primary: English and Bengali version of the KOOS questionnaire [39]. KOOS is a user-friendly, self-reported (patients' self-administered), valid and reliable questionnaire [40, 41] consisting of 42 questions in total addressing five patient-related domains including pain (9 questions), other disease-specific symptoms (7 questions), activity of daily living (ADL) (17 questions), sport and recreation function (5 questions), and knee-related quality of life (4 questions). All items are evaluated by five point Likert scale. Total score changes between 0 and 100. Higher scores indicate better function. It takes 5-10 min to fill in all questions. KOOS is in the public domain and is free of charge. There is no licensing or permission to use KOOS. KOOS includes Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) LK 3.0 in its complete and original format, and WOMAC scores can also be calculated [42]. The Minimal Important Change (MIC) is currently suggested to be 8-10. The minimal detectable changes are for KOOS Pain 6-6.1, for KOOS Symptoms 5-8.5, for KOOS ADL 7-8, for KOOS Sport/Recreation 5.8-12, and for KOOS QOL 7-7.2 [43]. An aggregate total score is not calculated since it is regarded desirable to analyze and interpret the five dimensions separately. For statistical purposes, when used as the primary outcome in an RCT, a single score can be constructed. In this case, the five individual subscale scores should be secondary outcomes [44].
2. Secondary:
    a) Five individual KOOS subscale scores – pain, other symptoms, ADL, sport/recreation, and QOL
    b) Frequency of add-on Paracetamol and/or NSAIDs (oral/topical) during study period of 6 months

Data collection: The outcomes will be assessed at baseline, after 3 months, and after 6 months. A specially designed Microsoft MS Office Excel 2007 spread sheet (master chart) will be used for data extraction and shall be subjected to statistical analysis.

Statistical techniques and data analysis: It will follow the intention-to-treat (ITT) approach; i.e. every included patient will enter the final analyses. Missing values will be imputed and replaced. Descriptive data (categorical and continuous) will be presented in terms of absolute values, percentages, mean, standard deviations (sd), confidence intervals (CI), etc. as appropriate. The groups will be checked for comparability of socio-demographic characteristics at baseline. Parametric or non-parametric inferential tests will be used to detect group differences as per normality or non-normality of distribution of data respectively. *P* values will be set at less than 0.05 two-tailed as statistically significant. SPSS® IBM® Inc., version 20 for Windows shall be used for statistical analysis. Aside

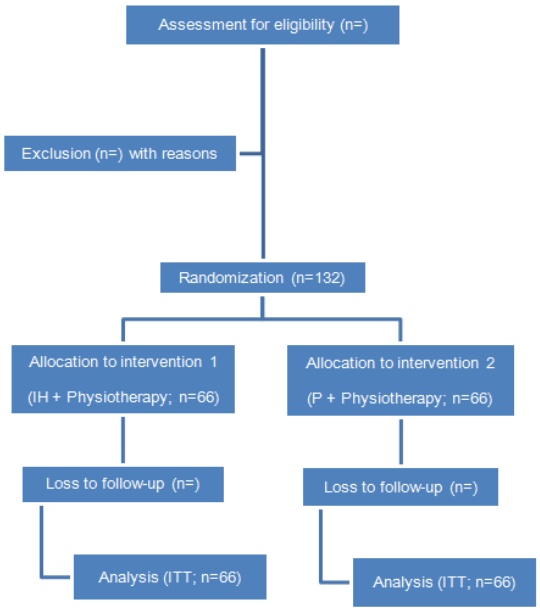
from the analysis of all randomized patients, a per-protocol analysis will also be carried out which is supposed to indicate which effect sizes can be reached under optimal circumstances. In the per-protocol sample, all patients will be included who fulfill all study requirements.

Ethical issues: Intercurrent illness, adverse or serious adverse event(s), if any, will be recorded and treated accordingly as per homoeopathic principles irrespective of the allocated codes, or if non-responding, then the patient shall be referred for conventional treatment. Prior to enrolment, each patient will be provided with a patient information sheet in local vernacular Bengali detailing the objectives, methods, risks and benefits of participating, and confidentiality issues. Subsequent to that, written informed consent shall be obtained. Approval is already taken from the institutional ethics committee (IEC) prior to initiation [5-23/NIH/PG/Ethical Comm. 2009/Vol 5/2691 (A/S); March 28, 2018]. The study shall be performed under the constant supervision of the IEC. In spite of using placebo in the control arm, standard physiotherapeutic measures will be advised to all the enrolled patients. This study is in compliance with the Helsinki Declaration and with the International Conference on Harmonization (ICH) – Good Clinical Practice. In case of necessary protocol amendments the amendment will be submitted to the ethics committee and competent authority and implementation will be done after approval.

DISCUSSION & CONCLUSION

Despite the fact that homoeopathy has a long tradition in the complementary treatment of patients and is part of the medical curriculum in many European universities, there is an ongoing debate on its efficacy, effectiveness and credibility. Thus, more robust clinical studies with clear and relevant endpoints are needed to substantiate the evidence base from primary to critical care. This study examines the

Study flow diagram:



efficacy of individualized homoeopathic medicines over placebo in knee OA in randomized design and prospectively for the first time toward providing clinical evidence.The use of homoeopathic medicines in knee OA is quite popular and respective publications have already been traced. This is a uni-centric study in a homoeopathy hospital. Although the treatment completely adheres to the respective guidelines, the setting might not be regarded as representative for integrative treatment of knee OA. The protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [45] and TIDieR (Template for Intervention Description and Replication) checklist [46]. Reporting of the study results will adhere to the criteria for reporting individualization in homoeopathy [47], the RedHot (homoeopathy specific CONSORT) statement [48] and model validity of homoeopathic treatment (MVHT) [49].

Should the main outcome of the trial be positive, the qualitative element of the study will provide insights into individualized homoeopathic treatment of knee OA which in turn will inform implementation of

homoeopathic medicines alongside physiotherapy measures. Publication of results in a peer-reviewed and indexed scientific journal and presentation at scientific meetings is planned. Due acknowledgement and/or authorship will be given to them who have participated in the proposal development and data analysis at the end of the paper with their specific contribution to the study. Authorship credit shall be based on substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

Trial status: At the time of initial manuscript submission, recruitment had already started (April 2018); and is ongoing.

Conflict of interest: The authors declare that they have no competing interests.

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Authors' contributions: S. Singh conceived and designed the study and remains the principal investigator. SAA is the co-investigator. MK and SS wrote the study protocol and are responsible for statistical analysis. SSA and AB are responsible for data compilation and management. DV, DD, DL, MA, NM, NK, SPS, SH, SBS and ZA are responsible for the homoeopathic part of the study. SS drafted the manuscript. All authors reviewed and approved the final manuscript.

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